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Single-Arm Phases 1 and 2 Trial of Niraparib in Combination With Pembrolizumab in Patients With Recurrent Platinum-Resistant Ovarian Carcinoma

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IMPORTANCE Patients with recurrent ovarian carcinoma frequently develop resistance to platinum-based chemotherapy, at which time treatment options become limited.

OBJECTIVE To evaluate the poly(adenosine diphosphate–ribose) polymerase (PARP) inhibitor niraparib combined with pembrolizumab in patients with recurrent ovarian carcinoma.

DESIGN, SETTING, AND PARTICIPANTS The TOPACIO/KEYNOTE-162 (Niraparib in Combination With Pembrolizumab in Patients With Triple-Negative Breast Cancer or Ovarian Cancer) trial, an open-label, single-arm phases 1 and 2 study enrolled women with advanced or metastatic triple-negative breast cancer (TNBC) or recurrent ovarian carcinoma, irrespective of *BRCA* mutation status. Median follow-up was 12.4 months (range, 1.2 to ≥23.0 months). Data were collected from April 15, 2016, through September 4, 2018, with September 4, 2018, as a data cutoff, and analyzed from September 4, 2018, through January 30, 2019.

INTERVENTIONS The recommended phase 2 dose (RP2D) was 200 mg of oral niraparib once daily and 200 mg of intravenous pembrolizumab on day 1 of each 21-day cycle.

MAIN OUTCOMES AND MEASURES The primary objectives of phase 1 were to evaluate dose-limiting toxic effects and establish the RP2D and dosing schedule. The primary objective of phase 2 was to assess objective response rate (ORR; complete plus partial responses). Results from the phase 1 ovarian carcinoma and TNBC cohorts and phase 2 ovarian carcinoma cohort are reported. Because of the similarity in the phase 1 and 2 ovarian carcinoma populations, the data were pooled to perform an integrated efficacy analysis.

RESULTS Fourteen patients (9 with ovarian carcinoma and 5 with TNBC) in phase 1 and 53 patients with ovarian carcinoma in phase 2 were enrolled, for a pooled ovarian carcinoma cohort of 62 patients (median age, 60 years [range, 46-83 years]). In the integrated efficacy phases 1 and 2 ovarian carcinoma population (60 of 62 evaluable patients), ORR was 18% (90% CI, 11%-29%), with a disease control rate of 65% (90% CI, 54%-75%), including 3 (5%) with confirmed complete responses, 8 (13%) with confirmed partial responses, 28 (47%) with stable disease, and 20 (33%) with progressive disease. The ORRs were consistent across subgroups based on platinum-based chemotherapy sensitivity, previous bevacizumab treatment, or tumor *BRCA* or homologous recombination deficiency (HRD) biomarker status. Median duration of response was not reached (range, 4.2 to ≥14.5 months). At data cutoff, 2 patients with a response and 1 patient with stable disease continued to receive treatment.

CONCLUSIONS AND RELEVANCE Niraparib in combination with pembrolizumab is tolerable, with promising antitumor activity for patients with ovarian carcinoma who have limited treatment options regardless of platinum status, biomarker status, or prior treatment with bevacizumab. Responses in patients without tumor *BRCA* mutations or non-HRD cancers were higher than expected with either agent as monotherapy.

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Editorial page 1103

Related article page 1132

Supplemental content

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Ovarian cancer is the eighth leading cause of deaths due to cancer worldwide, with a 5-year survival rate ranging from 30% to 50%. Although most patients initially have platinum-sensitive ovarian carcinoma, their disease eventually becomes resistant or refractory to platinum-based chemotherapy.[1,2] Some patients are unable to receive platinum-based chemotherapy owing to cumulative toxic effects or allergic reactions and receive non–platinum-based agents such as weekly paclitaxel, pegylated liposomal doxorubicin hydrochloride, or topotecan hydrochloride alone or in combination with bevacizumab.[3,4] Owing to the risk of vascular toxic effects and gastrointestinal tract perforation, bevacizumab is contraindicated in approximately one-third of patients[5]; non–platinum-based monotherapy in these patients results in low response rates (10%-15%) and short durations of response (3-4 months).[6]

The treatment armamentarium for ovarian carcinoma has recently been expanded to include poly(adenosine diphosphate–ribose) polymerase (PARP) inhibitors. PARPs are enzymes that detect DNA damage and promote repair by several mechanisms. Inhibition of PARP1/2 in cells that are already deficient in DNA repair mechanisms, such as those with *BRCA* (OMIM 113705 and 600185) mutations or homologous recombination deficiency (HRD), causes increased genomic instability and ultimately cell death. This synergism between cellular defect and drug-induced effect is termed *synthetic lethality*. Patients with *BRCA* wild-type (*BRCA*wt) tumors also benefit from PARP inhibition induced by niraparib; this effect is thought to be driven by high tumor accumulation of niraparib.[7] Niraparib is approved in the United States and European Union for the maintenance treatment of recurrent ovarian carcinoma for patients with a complete or partial response to platinum-based chemotherapy.[8,9] This approval was based on results from the European Network of Gynaecological Oncological Trial Groups (ENGOT)-OV16/NOVA trial,[10] which demonstrated that treatment with niraparib significantly improved progression-free survival along a graduated continuum. The strongest effect was observed in patients with germline *BRCA*-mutated (g*BRCA*mut) tumors (hazard ratio [HR], 0.27), followed by patients with HRD-positive/g*BRCA*wt tumors (HR, 0.38) and those with HRD-negative tumors (HR, 0.58).[10]

Programmed cell death receptor 1 (PD-1) is a checkpoint receptor that is expressed on activated T cells. Its associated ligands, programmed death-ligands 1 and 2 (PD-L1 and PD-L2), are frequently expressed on neoplastic cells. Ligand receptor binding results in downregulation of the immune response. Antibodies targeting PD-1 have emerged as promising therapies for several types of cancers by promoting T cell–mediated killing.[11] Preclinical models, including those for ovarian carcinoma, have demonstrated a synergistic antitumor effect with niraparib and anti-PD-1 drugs regardless of *BRCA* mutation status or PD-L1 expression.[12] The immunomodulatory function of niraparib has been proposed as a potential mechanism for this synergy based on the observation that niraparib treatment significantly increased the activities of the stimulator of interferon gene and interferon pathways and enhanced intratumoral immune cell infiltration and upregulation of granzyme B–positive T cells.[12,13] Other mechanisms, such as PARP inhibitor–mediated upregulation of PD-L1 expression, may also play a role in the activity of this combination.[14,15] The TOPACIO/KEYNOTE-162 (Niraparib in Combination With Pembrolizumab in Patients With Triple-Negative Breast Cancer or Ovarian Cancer) trial evaluated the hypothesis that niraparib combined with an anti-PD-1 antibody (pembrolizumab) would be safe and effective in populations with difficult-to-treat ovarian carcinoma.

Key Points

Question What is the clinical activity and safety of combination therapy of niraparib plus pembrolizumab in patients with platinum-based chemotherapy–resistant ovarian carcinoma or those not eligible for retreatment with a platinum-based chemotherapy?

Findings Sixty-two patients with ovarian carcinoma were enrolled in this open-label, single-arm phases 1 and 2 study. Among the 60 evaluable patients, 3 had complete responses, 8 had partial responses, and 28 had stable disease.

Meaning Combination niraparib plus pembrolizumab therapy showed promising antitumor activity in patients with ovarian carcinoma, warranting further investigation.

Methods

Study Design and Participants

This multicenter, open-label, single-arm phases 1 and 2 study evaluated the safety and efficacy of niraparib and pembrolizumab combination therapy in patients with previously treated advanced or metastatic triple-negative breast cancer (TNBC) or ovarian carcinoma (further details are available in eMethods in Supplement 1). Data were collected from April 15, 2016, through September 4, 2018. Patients were eligible regardless of *BRCA* mutation status. Herein, we report the phase 1 portion of the study (patients with TNBC or ovarian carcinoma) and the results from the phase 2 ovarian carcinoma cohort. Findings for the phase 2 cohort of patients with TNBC will be reported separately.

The phase 1 part of the study included a dose escalation to determine the recommended phase 2 dose (RP2D) and schedule of niraparib to be administered in combination with the recommended dose of pembrolizumab. Patients were enrolled at 34 sites in the United States. The study was conducted in accordance with ethical principles founded in the Declaration of Helsinki. The study protocol (available in Supplement 2) and/or other relevant documents received approval by the institutional ethics committee, institutional review board, and/or relevant competent authorities at each site. All patients provided written informed consent to participate in the study.

Procedures

Phase 1

We used a standard 6-plus-6 dose escalation design. Dosing was initiated with a cohort treated at the starting dose of

200 mg of oral niraparib once daily for days 1 to 21 and 200 mg of intravenous pembrolizumab on day 1 of each 21-day cycle (dose level 1). After a safety review, the next-higher dose level was opened for enrollment if less than one-third of patients in dose level 1 experienced a dose-limiting toxic effect (DLT) during cycle 1. Information on DLTs and related interventions are detailed in the eMethods in Supplement 1.

Once dose level 1 was determined to be safe, a cohort was enrolled at dose level 2 and treated with a combination of 300 mg of oral niraparib once daily and 200 mg of intravenous pembrolizumab once every 21 days. No further dose escalation for niraparib was planned. The maximum tolerated dose was defined as the highest dose with DLTs observed in less than one-third of patients during cycle 1 of combination treatment. The RP2D was based on an evaluation of multiple end points, including the DLT rate in first and subsequent cycles of combination treatment, the rate of dose modifications for non-DLT adverse events, the ability to manage toxic effects, pharmacokinetics, niraparib dose intensity, and signs of clinical efficacy.

Phase 2

All patients in phase 2 began treatment with the RP2D from the phase 1 portion. Additional on-treatment assessments were conducted in cycle 1 on days 8 and 15 and on day 1 of all subsequent cycles. Safety assessments conducted throughout the treatment period included physical examination, measurement of vital signs, electrocardiography, Eastern Cooperative Oncology Group performance status, and clinical laboratory assessments (complete blood cell count, blood chemical evaluation, thyrotropin level, thyroid function tests, urinalysis, cancer antigen-125 level, and pregnancy tests).

Radiographic evaluations to assess the extent of disease were conducted every 9 weeks after day 1 of cycle 1 during study treatment and/or at any time when progression of disease was suspected. After 1 year of radiographic assessments, patients had imaging performed every 12 weeks until disease progression. If a patient discontinued treatment for a reason other than disease progression, death, withdrawal of consent, or loss to follow-up, scans and cancer antigen-125 testing continued at the specified intervals. Per the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1),[16] patients who achieved a complete response or a partial response had the response confirmed with tumor imaging no earlier than 4 weeks after the first indication of response or at the next scheduled scan (ie, 9 weeks later), whichever was clinically indicated. Adverse events were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Biomarker testing is described in eMethods in Supplement 1.

Outcomes

The primary objectives of phase 1 were to establish the RP2D and dosing schedule of the niraparib and pembrolizumab combination and to evaluate DLTs during the first cycle of treatment. The primary objective of phase 2 was to estimate the clinical activity of combination treatment with niraparib and pembrolizumab in terms of objective response rate (ORR; the best of complete or partial responses) assessed by the investigators using RECIST 1.1. Secondary end points included duration of response, disease control rate (best response of complete or partial responses or stable disease), and progression-free survival, all by RECIST 1.1, and overall survival. Correlation of tumor *BRCA* (t*BRCA*) mutation status and HRD status with other immune-related biomarkers and with efficacy outcomes were exploratory end points.

Statistical Analysis

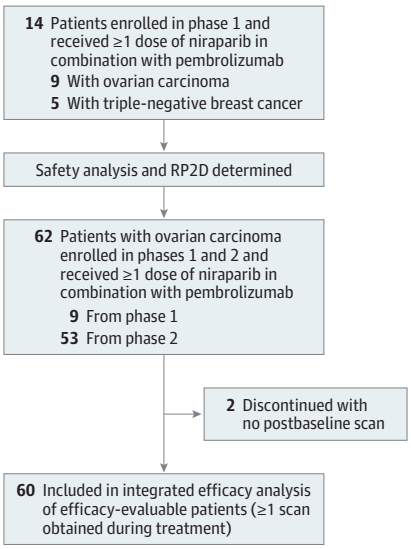
Data were analyzed from September 4, 2018, through January 30, 2019. Demographics, baseline characteristics, and safety results were summarized descriptively. Response end points were evaluated using the full analysis set, defined as all patients in phase 1 and phase 2 with ovarian carcinoma who received any amount of study medication, as well as the efficacy-evaluable analysis set, which included patients who received any amount of study treatment and who had at least 1 evaluable postbaseline tumor assessment. Target enrollment of 48 patients was estimated to provide 82% power to rule out the null hypothesis (≤15% ORR) when the true ORR was 30% at the 1-sided 5% type I error rate. Assuming that the true ORR was 35%, enrollment of 48 patients was estimated to provide 94% power. Point estimates and 2-sided 90% CIs were provided for the analysis of ORR and disease control rate. For time-to-event end points, the median and corresponding 2-sided 95% CI were obtained using Kaplan-Meier methods. Exploratory subgroup analyses were performed by biomarker status (t*BRCA*, HRD, and PD-L1), response to last platinum-based chemotherapy (resistant, refractory, or not applicable), number of lines of prior therapy, and prior bevacizumab use using the efficacy-evaluable analysis set. Platinum-free interval (PFI) was defined as the time between the end of the last platinum-based chemotherapy to progression. Using the PFI, response to the last platinum-based chemotherapy was classified as follows: platinum refractory (PFI, ≤28 days), platinum resistant (PFI, 29-179 days), and not applicable (due to toxic effects or allergic reaction; PFI, ≥180 days).

All statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc). A data cutoff date of September 4, 2018, was used.

Results

From April 2016 through September 2017, 14 patients (9 with ovarian carcinoma and 5 with TNBC) in phase 1 and 53 patients with ovarian carcinoma in phase 2 were enrolled and received the initial dose of study treatment (median age, 60 years; range, 46-83 years). At the time of the data cutoff, 3 patients with ovarian carcinoma continued to receive treatment. Fifty-nine patients with ovarian carcinoma discontinued treatment because of radiologic disease progression in 41, clinical disease progression in 8, an adverse event in 5, patient request in 4, and a move out of the country in 1 (**Figure 1**).

Figure 1. Enrollment, Treatment, and Outcomes



RP2D indicates recommended phase 2 dose.

Based on the safety profiles and observed DLTs at dose levels 1 and 2 (eTable 1 in Supplement 1), the RP2D of oral niraparib was determined to be 200 mg once daily in combination with 200 mg of intravenous pembrolizumab once every 21 days. The demographics and baseline characteristics were similar in patients in phases 1 and 2 (eTable 2 in Supplement 1); combined data are shown in **Table 1**.

Because of the similarity in the phases 1 and 2 ovarian carcinoma populations, the data were pooled to perform an integrated efficacy analysis. In the combined phases 1 and 2 ovarian carcinoma full-analysis population (n = 62), 3 patients had confirmed complete responses, 8 had confirmed partial responses, 28 had stable disease, 20 had progressive disease, and 3 were not evaluable. The confirmed ORR of the combined population was 18% (90% CI, 10%-28%). Of the 3 patients not evaluable in the full-analysis set, 2 discontinued before the first scan during treatment was conducted (both owing to patient request), and an additional patient (included in the efficacy-evaluable population) had a postbaseline scan demonstrating stable disease, but response was not evaluable because the duration requirement was not met. Four of the patients with stable disease had a partial response that was not confirmed by a subsequent scan. In the efficacy-evaluable population (n = 60), the confirmed ORR of the combined population was 18% (90% CI, 11%-29%), with a disease control rate of 65% (90% CI, 54%-75%) (**Table 2** and **Figure 2**A-C).

Median duration of follow-up was 12.4 months (range, 1.2 to ≥23.0 months). In patients with ovarian carcinoma and a confirmed complete or partial response, the median duration of response had not been reached at the time of the data cutoff (range, 4.2 to ≥14.5 months) (eFigure in Supplement 1). Eight patients with partial or complete responses had a duration of response lasting longer than 6 months, 4 of whom achieved duration of longer than 9 months (Figure 2B). In addition, 5 of these 8 patients with long-term responses had platinum-refractory or platinum-resistant disease and t*BRCA*wt tumors. Two of these patients were continuing treatment at the time of data cutoff. Nine patients with stable disease received treatment for longer than 6 months; of these, 1 received treatment for at least 12.5 months (ongoing) and 1, for 13.2 months.

Exploratory analyses of biomarker subpopulations indicate that the combination treatment of niraparib and pembrolizumab resulted in antitumor activity across the study

Table 1. Patient Characteristics at Baseline

Characteristic	Combined Phases 1 and 2 Patients With Ovarian Carcinoma (n = 62)
Age, median (range), y	60 (46-83)
ECOG performance status, No. (%)[a]	
0	44 (71)
1	18 (29)
Prior lines of therapy, median (range)	3 (1-5)
Prior bevacizumab, No. (%)	39 (63)
Prior chemotherapy, No. (%)[b]	
Anthracycline	40 (65)
Cyclophosphamide	5 (8)
Gemcitabine hydrochloride	29 (47)
Paclitaxel	61 (98)
Platinum	62 (100)
Topotecan hydrochloride	3 (5)
Platinum status, No. (%)	
Resistant	30 (48)
Refractory	17 (27)
Not applicable[c]	15 (24)
t*BRCA* status, No. (%)	
BRCA1 mutation	9 (15)
BRCA2 mutation	2 (3)
BRCA wild type	49 (79)
Unknown	2 (3)
HRD status, No. (%)	
HRD positive	22 (35)
HRD negative	33 (53)
HRD unknown	7 (11)
PD-L1 status, No. (%)[d]	
Positive	35 (56)
Negative	21 (34)
Unknown	6 (10)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HRD, homologous recombination deficiency; PD-L1, programmed death-ligand 1; t*BRCA*, tumor *BRCA*.

[a] Zero indicates fully active and able to perform all predisease activities without restriction; 1, restricted in strenuous activity yet ambulatory and able to do light work.

[b] Includes chemotherapy used in more than 1 patient; those used in only 1 patient are not listed.

[c] Includes patients with an interval free of platinum-based chemotherapy of at least 180 days but unable to receive further platinum-based chemotherapy (owing to toxic effect or allergic reaction).

[d] Positivity was based on a combined positive score of 1 provisional cutoff by immunohistochemistry.

population regardless of t*BRCA* mutation or HRD status (Figure 2A). The ORRs for all biomarker-identified populations appeared to be similar (**Table 3**). A subgroup analysis of additional baseline characteristics, including tumor PD-L1 status, did not reveal any specific marker that drove clinical activity from the combination treatment regimen. Although we noted that patients with fewer lines of therapy had higher response rates than those with 3 or more prior lines, the CIs overlapped. Response rates were similar regardless of platinum status or prior bevacizumab treatment. In this study, 39 patients (63%) had previously received treatment with bevacizumab. Similar ORRs were observed in patients who had received bevacizumab compared with those who did not (19% [90% CI, 9%-33%] vs 17% [90% CI, 6%-36%]).

In all treated patients, the median progression-free survival was 3.4 months (95% CI, 2.1-5.1 months), with 6- and 12-month progression-free survival estimated to be 31% and 12%, respectively (Figure 2C). The overall survival data were not mature at the time of this analysis.

The most common treatment-related adverse events of any grade (n = 53) in phase 2 were fatigue (28 [53%]), nausea (22 [42%]), anemia (19 [36%]), and constipation (19 [36%]) (eTable 3 in Supplement 1). The most common treatment-related adverse events of at least grade 3 were anemia (11 [21%]) and thrombocytopenia (5 [9%]). In addition, the most common adverse effects of laboratory investigations of at least grade 3 were decreased platelet count (3 [6%]), decreased white blood cell count (3 [6%]), and decreased neutrophil count (2 [4%]). No treatment-related patient deaths or cases of myelodysplastic syndrome or acute myeloid leukemia occurred. Immune-related adverse events were defined as the adverse events of clinical interest that have been commonly associated with pembrolizumab.[17] Immune-related adverse effects deemed associated with treatment by the investigator occurred in 10 patients (19%); immune-related adverse effects of grade 3 or greater occurred in 3 patients (6%) (eTable 3 in Supplement 1). Immune-related adverse effects of any grade regardless of causality occurred in 14 patients (26%) and of at least grade 3 in 4 (8%). The only grade 3 immune-related adverse effect regardless of causality that occurred in 2 or more patients was hyperglycemia in 2 patients (4%): 1 with a history of diabetes and 1 with hyperglycemia at screening that worsened during treatment. No grade 4 immune-related adverse effects occurred.

Table 2. Integrated Efficacy Analysis of ORR for Phases 1 and 2

Best Overall Response	Response Data (n = 60)
Complete response, No. (%)	3 (5)
Partial response, No. (%)	8 (13)
Stable disease, No. (%)[a]	28 (47)
Progressive disease, No. (%)	20 (33)
Inconclusive, No. (%)[b]	1 (2)
ORR, % (90% CI)[c]	18 (11-29)
DCR, % (90% CI)[d]	65 (54-75)

Abbreviations: DCR, disease control rate; ORR, objective response rate.

[a] Four patients had an unconfirmed partial response.

[b] One patient had an evaluable postbaseline scan but was not evaluable for response; the postbaseline scan demonstrated stable disease and was therefore included in the efficacy-evaluable analysis set. However, minimum duration requirement of stable disease was not met.

[c] Includes patients with complete and partial responses.

[d] Includes patients with complete and partial responses and stable disease.

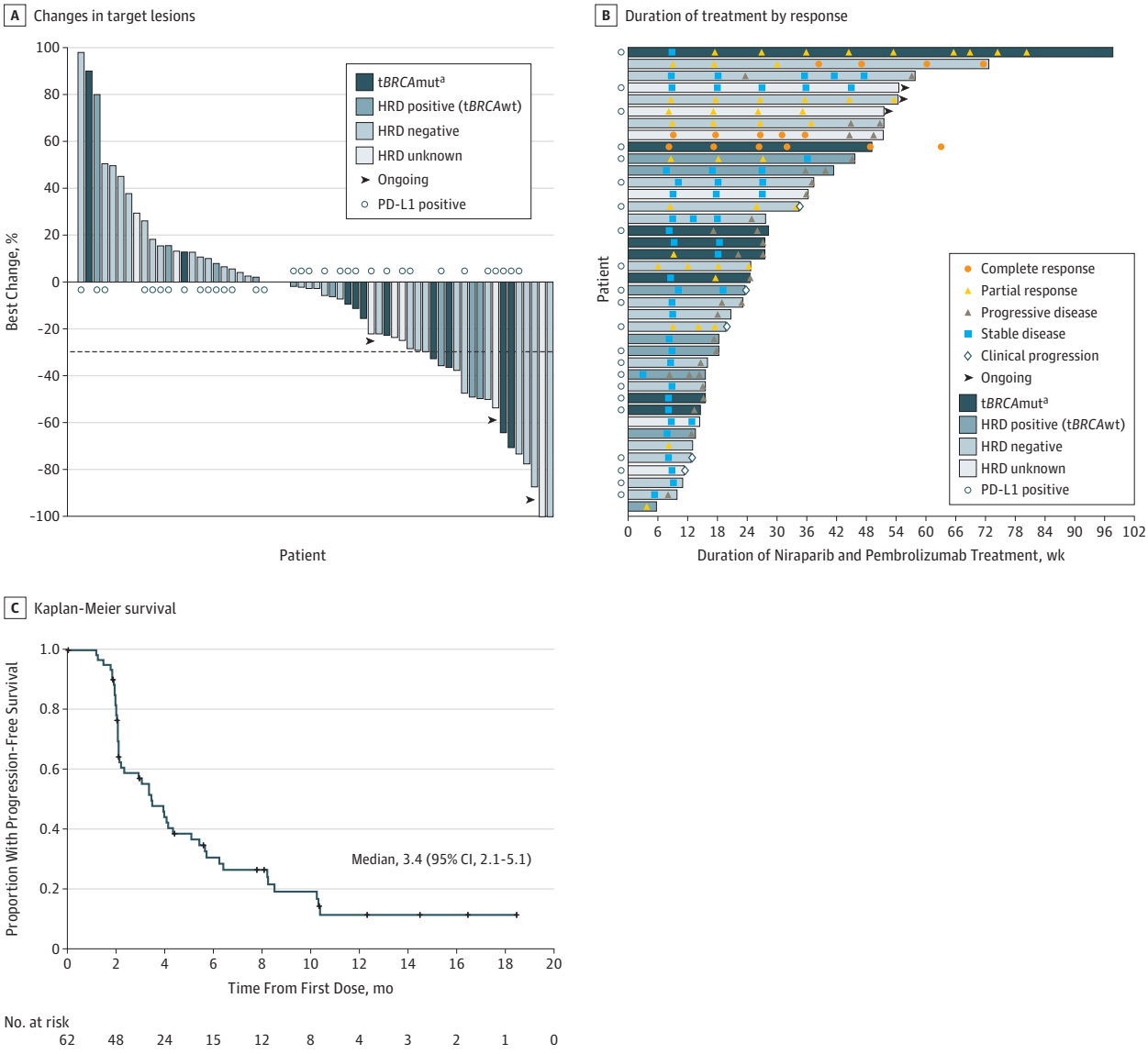
Discussion

This study has shown that the combination treatment of niraparib and an anti-PD-1 antibody appears to be well tolerated and potentially provides clinical activity by tumor shrinkage and disease stabilization in patients with recurrent ovarian carcinoma. No new toxicity signals were observed, and the regimen could represent a potential new therapeutic option in this patient population.

The study patient population was clinically diverse; most had tumors that were t*BRCA*wt, had been previously treated with bevacizumab, and had acquired platinum-resistant or platinum-refractory disease. Response rates and stable disease rates were similar across the biomarker-defined populations as defined by t*BRCA* mutation and HRD status. Single-agent PARP inhibitors have demonstrated an ORR of approximately 25% to 30%[18,19] in patients with platinum-resistant ovarian carcinoma and a *BRCA* mutation, but limited activity has been observed in patients with *BRCA* mutations and platinum-refractory disease (0%-14%).[20,21] The efficacy of PARP inhibitor monotherapy is even lower for patients who lack a *BRCA* mutation and have platinum-resistant (ORR, approximately 5%)[22,23] or platinum-refractory (ORR, 0%) ovarian carcinoma.[24] Similarly, single-agent PD-1/PD-L1 inhibitors have an ORR of 4% to 10% in platinum-resistant ovarian carcinoma irrespective of PD-L1 expression levels.[11,25,26] The combination of anti-PD-1 antibody and niraparib appears to improve efficacy in the t*BRCA*wt (ORR, 19%) and non-HRD (ORR, 19%) patient populations when compared with monotherapy with either agent. Given the modest activity of PD-1/PD-L1 inhibitors in ovarian carcinoma, trials of combinations of PD-1/PD-L1 antibodies with antiangiogenic agents, chemotherapy, and targeted agents are being developed and/or have been reported. As an example, the combination of nivolumab and bevacizumab was associated with an ORR of 11% in platinum-resistant ovarian carcinoma,[27] and the combination of avelumab and doxorubicin was associated with an ORR of 13.3%.[28] Although previous trials[23,29] have shown that platinum status and response rates to PARP inhibitors are correlated, patients in our study with reduced sensitivities to platinum also showed clinical activity. Notably, 5 of the 8 patients who had a duration of response lasting more than 6 months had platinum-refractory or platinum-resistant ovarian carcinoma and t*BRCA*wt tumors.

Benefit from immunotherapy can manifest itself via prolonged periods of stable disease in patients. In this study, 9 patients with stable disease received treatment for more than 6 months, 2 of whom received treatment for longer than 1 year. This finding suggests that this combination therapy may be of

Figure 2. Antitumor Activity of Niraparib in Combination With Pembrolizumab



Responses were confirmed using Response Evaluation Criteria in Solid Tumors, version 1.1. HRD indicates homologous recombination deficiency; PD-L1, programmed death-ligand 1; t*BRCA*mut, tumor *BRCA* mutated; and t*BRCA*wt, tumor *BRCA* wild type.

[a] All patients with t*BRCA*mut also had HRD-positive disease.

therapeutic value even in patients who do not achieve a RECIST 1.1 response.

Most patients in this study had previously received treatment with bevacizumab. Importantly, this treatment did not affect outcomes; responses were similar in patients who had received bevacizumab compared with those who did not. Because the combination of chemotherapy and bevacizumab is the standard of care for patients with recurrent ovarian carcinoma, most of these patients will receive this treatment at some point in their disease; therefore, it is important that the efficacy of therapies given in later lines is not detrimentally affected by prior bevacizumab treatment. The current standard of care for patients with platinum-resistant ovarian carcinoma treated with prior bevacizumab is non-platinum-based chemotherapy, which has response rates of less than 10%.

The incidence of thrombocytopenia of any grade or of grade 3 or higher was substantially lower in this study than in other niraparib trials.[10] This finding is likely due to the lower 200-mg dose of niraparib once daily that was selected as the RP2D when administered in combination with pembrolizumab. Compared with the 300-mg dose of niraparib, the 200-mg dose has been found to reduce the incidence of thrombocytopenia in patients with recurrent ovarian carcinoma and a baseline body weight of less than 77 kg and baseline platelet count of less than $150 \times 10^3/\mu L$.[30] No additional safety con-

Table 3. ORR Subgroup Analysis in the Efficacy-Evaluable Population

Patient Subgroup	No./Total No. of Patients	ORR, % (90% CI)[a]
All	11/60	18 (11-29)
Platinum status		
Resistant	6/29	21 (9-37)
Refractory	2/16	13 (2-34)
Not applicable[b]	3/15	20 (6-44)
Prior lines of therapy[c]		
1-2	7/25	28 (14-46)
≥3	4/35	11 (4-24)
Prior bevacizumab use		
Yes	7/37	19 (9-33)
No	4/23	17 (6-36)
t*BRCA* status[d]		
t*BRCA*mut	2/11	18 (3-47)
t*BRCA*wt	9/47	19 (10-31)
PD-L1 status[d]		
Positive	7/33	21 (10-36)
Negative	2/21	10 (2-27)
HRD status[d]		
HRD positive	3/21	14 (4-33)
HRD negative	6/32	19 (9-34)

Abbreviations: HRD, homologous recombination deficiency; ORR, objective response rate; PD-L1, programmed death-ligand 1; t*BRCA*, tumor *BRCA*; t*BRCA*mut, tumor *BRCA* mutation; t*BRCA*wt, tumor *BRCA* wild type.

[a] Includes only confirmed responses using Response Evaluation Criteria in Solid Tumors, version 1.1.

[b] Includes patients with an interval free of platinum-based chemotherapy of at least 180 days but unable to receive further platinum-based chemotherapy (owing to toxic effects or allergic reaction).

[c] For pooled analysis, neoadjuvant therapy, adjuvant therapy, and the combination of both were considered to be 1 line of therapy. Small molecules, hormonal agents, and bevacizumab were not counted in the lines of therapy.

[d] Only patients with known biomarker status were included.

cerns due to immune-related adverse events were noted. The values for immune-related adverse events regardless of causality (any grade, 26%; grade ≥3, 8%) are comparable to those from a study of pembrolizumab monotherapy for PD-L1-positive non–small cell lung cancer (any grade, 29.2%; grade ≥3, 9.7%; treatment-related, immune-related adverse events were not reported). No new safety signals were observed with the combination treatment of niraparib and pembrolizumab compared with the safety profiles of either drug as monotherapy.

Limitations

This study was a signal-seeking phase 2 trial with 62 patients with ovarian carcinoma enrolled; therefore, the results presented herein will need to be validated in a larger trial. Although the predefined statistical criteria for this study were not met (null ≤15%), the observed ORR is of interest, especially in the t*BRCA*wt and non-HRD patient populations; durable responses were observed across platinum status, t*BRCA* mutations, and tissue HRD status (although patient numbers in the various subgroups are relatively small).

Conclusions

Niraparib in combination with a PD-1 inhibitor showed promising activity for patients with platinum-resistant and platinum-refractory recurrent ovarian carcinoma, particularly in patients with t*BRCA*wt or non-HRD disease, regardless of prior bevacizumab treatment. No new safety signals were identified; hematologic adverse events were minimized with a 200-mg starting dose of niraparib in the phase 2 portion of this study.

ARTICLE INFORMATION

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